Conditional Survival after Trimodality Therapy for Esophageal Cancer: A Re-evaluation of Prognostic Factors Over Time

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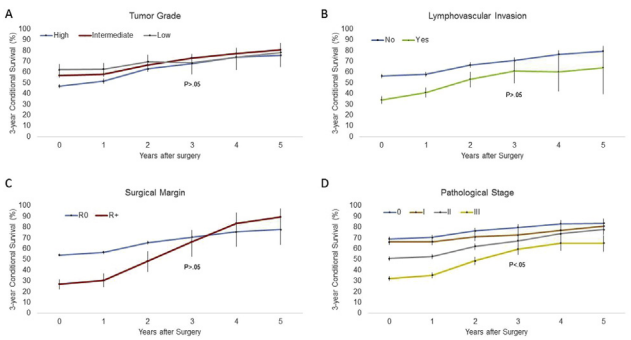
INTRODUCTION: Overall survival (OS) does not account for dynamic changes in prognosis over time. Conditional survival (CS) describes the probability a patient will survive an additional period of time, given they have already survived a certain number of years. Our objectives were to report OS and CS after trimodality therapy for esophageal cancer and report factors associated with survival.

METHODS: Patients completing trimodality therapy for esophageal cancer were identified within the National Cancer Database (2006-2016). OS was calculated from surgery and 3-year CS estimates were measured. Multivariable Cox regression models were constructed to identify factors associated with OS and CS.

RESULTS: In total, 8,609 patients were included. The 5-year OS was 41.4%. For patients surviving 2 and 3 years after operation, the 3-year CS was 65.2% and 70.6%, respectively. In multivariable analyses, patients with older age, higher tumor grade, lymphovascular invasion, and positive surgical margins had worse OS (all; $p < 0.05$). However, in CS analyses 3-years after operation, only age continued to be associated with worse survival. Compared with patients with a pathologic complete response, increasing stage was strongly associated with worse OS ($p < 0.05$) and CS (stage I: hazard ratio [HR] 1.31; 95% CI, 1.04 to 1.65; stage II: HR 1.65; 95% CI, 1.37 to 2.00; stage III: HR 2.39; 95% CI, 1.92 to 2.96) (Fig. 1).



Figure

CONCLUSION: With the exception of pathologic stage, several factors traditionally associated with worse survival after esophagectomy appear to no longer be meaningful in patients surviving several years after surgery. These findings have important implications in patient surveillance and survivorship.

Danger in America's Small Towns: Rural-Urban Survival Disparities for Patients with Surgically Treated Lung Cancer

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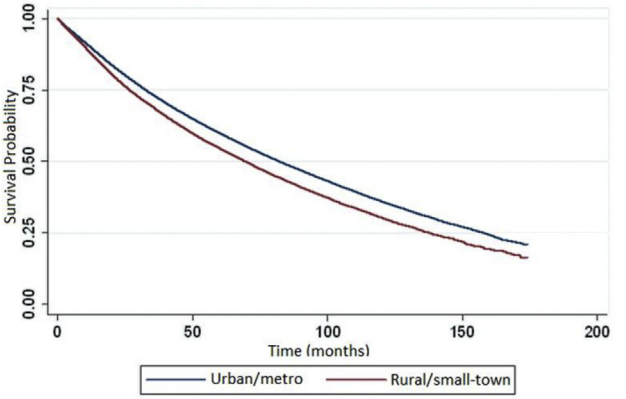
INTRODUCTION: Non-small cell lung cancer (NSCLC) is a common cancer diagnosis among patients living in rural areas and small towns who face unique challenges accessing care. We examined regional differences in survival for rural patients compared with those from urban and metropolitan areas.

METHODS: The National Cancer Database was used to identify surgically treated patients with NSCLC from 2004 to 2016. Patients from rural and small town counties were compared with urban and metropolitan counties. Differences in patient sociodemographic, clinical, hospital, and travel distance characteristics were described using chi-square tests. Kaplan-Meier methods with log-rank tests and Cox proportional hazards analysis was used to examine differences in mortality.

RESULTS: The study included 380,281 surgically treated NSCLC patients with 12.0% (n = 45,473) categorized as rural/small town. Rural/small town patients traveled farther for treatment and were from areas characterized by lower income and educational attainment (all, $p < 0.001$). Survival probabilities for rural/small-town patients were worse at one year (85% vs 87%), five years (48% vs 54%), and ten years (26% vs 31%) (all, $p < 0.001$). Living in a rural/small-town location remained an independent risk for death (HR 1.07; 95% CI, 1.04 to 1.10) after controlling for cancer stage, patient and hospital characteristics, and travel distance. Risk of death also increased as distance



*p <0.001

Figure. Title: Kaplan-Meier model results for differences in survival of surgically treated NSCLC patients, National Cancer Database 2004-2016*. Similar differences are seen when analysis is performed by stage.

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from the treating facility increased (HR 1.10; 95% CI, 1.06 to 1.14).

CONCLUSION: Rural and small-town patients with surgically treated NSCLC had worse survival outcomes compared with urban and metropolitan patients independent of other risk factors. Better understanding the drivers of observed outcomes differences can provide meaningful opportunities for improvement.

Evaluation of a Novel GCP2-targeted Tracer for the Intraoperative Molecular Imaging of Pulmonary Squamous Cell Carcinoma

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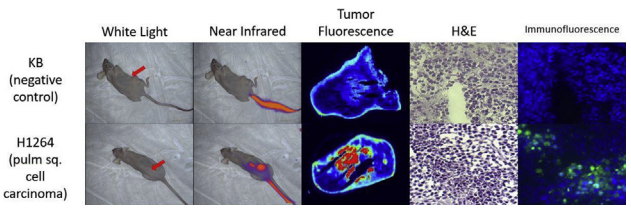
INTRODUCTION: Intraoperative molecular imaging (IMI) using fluorescent, tumor-targeted tracers to identify malignant cells is effective in improving the completeness of resection for many tumor types. However, there is a major unmet need in pulmonary squamous cell carcinoma. We sought to develop a receptor-targeted tracer for IMI of pulmonary squamous cell carcinoma.

METHODS: A glutamate carboxylase type II (GCP)-targeted probe, GCP2-S0456 was developed given known overexpression in pulmonary squamous cell carcinoma. To establish a murine model, athymic nude mice were injected with 5.0×10^6 of H1264 cells, a pulmonary squamous cell line expressing GCP2. The nasopharyngeal carcinoma cell line, KB, was the negative control. Once tumors reached 300 to 400 mm^3 in volume, animals (5 mice/group) were injected with 10 nM GCP2-S0456 diluted in 100 μL saline. Two hours after injection, mice were imaged, sacrificed, and organs were harvested.

RESULTS: Spectroscopic analysis showed that the absorption and emission wavelengths of GCP2-S0456 were 776 nm and 793 nm, respectively. On biodistribution analysis, GCP2-S0456 accumulated in the kidneys of all mice (mean signal-to-background ratio [SBR] 8.86) without other organ involvement. GCP2-S0456 selectively accumulated in mice bearing H1264 tumors (mean SBR 6.48), but no fluorescent signal was seen in KB tumors (mean SBR 0.89). Immunohistochemical and histopathological analysis confirmed the selective accumulation of the dye in the tumor compared with background healthy tissue. There were no adverse effects attributable to GCP2-S0456 administration.

CONCLUSION: GCP2-S0456 is a safe and effective tracer for IMI of pulmonary squamous cell carcinoma and there is clear promise for clinical translation.



Figure

Fetal Pulmonary Genome Modification via Direct Intratracheal Injection in the Mouse

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INTRODUCTION: The fetal pulmonary system is an attractive target for gene and drug therapy due to a naïve/tolerant immune system, absent mucous barrier, and abundance of proliferating progenitors. A previous publication described intratracheal delivery of dye or viral reporter particle in the fetal mouse. We optimized the technique to deliver gene modifying mRNA and characterized cellular targeting, which demonstrates the potential to correct congenital pulmonary disease.

METHODS: Time-dated mTmG dams, in which gene modification activates GFP expression, underwent laparotomy and uterine exposure. Embryonic day 17 fetal heads were exteriorized. Tracheae were dissected and injected with 30 μL vehicle containing mRNA. Fetal heads were reduced, amniotic fluid was replaced with saline, laparotomies were closed, and dams were recovered. After vaginal delivery, lungs and cell subpopulations were evaluated for GFP expression at day of life 1.

RESULTS: The maximum number of fetuses injected per pregnancy was 3 with a total operative time under 1 hour and overall fetal survival of 90%. GFP was detectable in large and small airways via fluorescence microscopy (Fig. 1). Representative flow cytometry demonstrated GFP expression approximately 4% overall that was most pronounced in epithelial cells (11.6%) followed by endothelial cells (2.2%) and mesenchymal cells (1.6%).

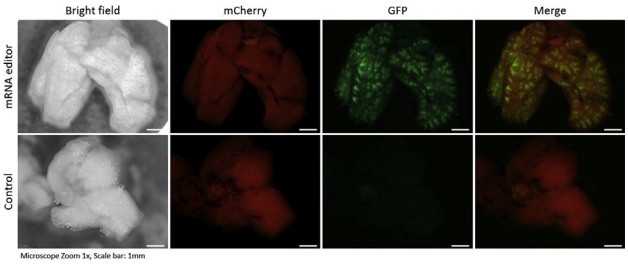

Figure 1. E17 mTmG fetuses injected IT with 30ul of mRNA harvested two days later at P1. Age matched control mTmG.